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The healthy sodium channel (Nav)-rich node of Ranvier axolemma is a precision, far-from-equilibrium entity, and its nano-structure, not surprisingly, is vulnerable to insult. Nodal excitability is easily perturbed by trauma, ischemia, and inflammation, all of which injure plasma membranes through combinations of blebbing, ATP-depletion, high-Ca^{2+} and reactive oxygen species. Injury-related dysfunction ranges from subthreshold oscillations (STO), to ectopic excitation, to propagation block. We showed that blebbing injury to recombinant Nav-bearing membranes (the nodal isoform Nav1.6) results in a coupled hyperpolarizing-shift of activation and availability, and computationally, we showed that the expected left-shifted I_{window} could rapidly dissipate ion gradients while impairing excitability. Interestingly, CA1 neurons subjected to prolonged epileptic discharge show I_{window} left-shift (Sun et al 2006 Acta Pharmacol Sin 27:1537) as if their membranes are injured. We assume here that where mild nodal damage occurs, injury-induced left-shift intensities will be ''smeared out'' over some fraction of the node's total Nav population. Computationally, we explored the modes of spontaneous activity that emerged for such scenarios. Since Na/K pump function would also suffer with membrane injury, we varied maximal pump activity. STOs mediated by reversal potential oscillations were a prominent feature of ''mild trauma''. Even as the firing threshold gradually depolarized, STOs kept triggering ectopic action potentials. Noise inputs at the injured node, we found, not only induced bursts but influenced their rates and durations. Finally, propagation abnormalities (e.g. non-1:1 transmission) along a 7-node axon whose middle node was injured, were explored with no input at the initial segment, with constant current input and with pulses that follow a Poisson distribution of arrival times.

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Estimation of Population-Specific Synaptic Currents from Laminar Multielectrode Local Field Potential Recordings

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Multielectrode array recordings of extracellular electrical field potentials along the depth axis of the cerebral cortex is an up-and-coming approach for investigating activity of cortical neuronal circuits (Einevoll et al., J. Neurophysiol., 2007; Blomquist et al., PLoS Comp. Biol., 2009). The low-frequency band of extracellular potential, i.e., the local field potential (LFP), is assumed to reflect the synaptic activity and can be used to extract the current source density (CSD) profile. However, physiological interpretation of CSD profile is uncertain because it does not disambiguate synaptic inputs from passive return currents or identifies population-specific contributions to the signal thus obfuscating its interpretation in terms of the excitation flow in the columnar microcircuit.

Here we present a novel anatomically informed model for decomposing the LFP signal into population-specific contributions and for estimating the corresponding laminar profiles of synaptic inputs. This involves a combination of 1) the linear forward model, which predicts population-specific laminar LFP in response to synaptic inputs applied to the population of cells having realistic morphologies; and 2) the linear inverse model, which reconstructs laminar profiles of synaptic inputs from laminar LFP data based on the forward prediction. Assuming spatial correlation of synaptic inputs within individual populations, the model decomposes the columnar LFP into population-specific contributions and estimates the corresponding synaptic input laminar profiles less the mean value. Constraining the solution with a priori knowledge of the spatial distribution of synaptic connectivity further allows estimating the strength of active synaptic projections from the columnar LFP profile thus fully specifying synaptic inputs.

The capability of the model is demonstrated by applying it to the experimental extracellular data.

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The Cofilin Signaling Pathway in Dendritic Spines

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Synaptic efficacy is regulated by the morphological and electrophysiological characteristics of dendritic spines. Long-term potentiation (LTP) is an increase in efficacy driven by the recruitment of AMPA receptors (AMPARs) and an increase in spine volume, while long-term depression (LTD) is a decrease in efficacy driven by the loss of AMPARs and a decrease in spine volume. Recent experimental evidence suggests that transient changes in cofilin activity are responsible for the morphological changes observed during LTP and LTD. The cofilin signaling pathways through LIM kinase (LIMK) and Slingshot (SSH) are well-established in several cell types, but their roles in synaptic plasticity are less well understood. Experiments focused on the LIMK pathway have produced contradictory results, and the SSH pathway has received almost no attention. Here we present a Virtual Cell model of the cofilin signaling pathway in dendritic spines. The upstream events include calcium-induced activation of CaMKII and Rho GTPases, which act through LIMK and Slingshot to regulate cofilin activity. The model outputs include changes in AMPAR density and F-actin content in dendritic spines. The model is implemented in an idealized, 3D analytic geometry, which allows us to explore the roles geometric confinement and protein localization. Membrane localization of certain signaling complexes generates a steep gradient of cofilin activity, which produces a highly dynamic outer ''shell'' of F-actin and a more stable ''core,'' as seen experimentally. Transient changes in cofilin activity are required for both AMPAR regulation and for F-actin dependent morphological changes, although these two effects can be decoupled under certain perturbations. We find that crosstalk between the LIMK and SSH pathway produces unintuitive behavior which may account for the seemingly contradictory results in the LIMK experiments. (Supported by NIH grant P41 RR013186.)

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Relation Between the Information Carrier in Nervous Systems and the Dependence of a Neuron Model Behavior on the Past Activity

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A neuron or neural network is in the transient regime if its input changes much faster than the convergence speed to its asymptotic dynamics. Transient dynamics are also related to the problem about the information carriers in nervous systems since spikes contain encoded information in the transient regime. Some studies have showed that neurons or neural networks function in the transient regime. Since transient dynamics can occur far from the invariant structure of a neuron or neural network, it is necessary to understand the dynamics of the entire phase space.

In this study, we analyze the global dynamics of an impulse-driven radial isochron clock, which is one of the canonical models of neuronal oscillators. We analyze the dynamics of the entire phase space using the Markov operator, denoting the density evolution of the neuronal oscillator. To construct the Markov operator, we use the asymptotic expansion of stochastic processes. We show that the Markov operator can successfully approximate the density evolution of the neuronal oscillator. We analyze the dynamics of the neuronal oscillator using the transient and the stationary properties of the Markov operator. We show that the second eigenvalue of the product of the Markov operators reflects the past activity of the neuronal oscillator; in other words, it describes the degree to which the current state of the neuronal oscillator is affected by past activity and how the model conveys this historical information.

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Volume Control in the PVN: A Role for TRPV4

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The hypothalamus is responsible for maintaining body fluid osmolarity within a narrow range (~290-300mOsm)[1]. Upon hypotonic challenge, increased heart rate, blood pressure and renal sympathetic activity have been seen[2]. The paraventricular nucleus (PVN) has been implicated as having a major role in osmoregulation. Treatment with hypertonic solutions has shown increases in action potential (AP) frequencies within parvocellular neurons[3]. The transient receptor potential vanilloid channel TRPV4 is a possible candidate for volume sensing within the PVN as it has this role in other tissues [4]. APs were recorded in brain slices using cell-attached patch clamp electrophysiology to investigate the mechanisms of osmoregulation within the parvocellular PVN. Results are given as a normalised mean ± SEM, significances were assessed by paired t-test. We also modelled the action of TRPV4 in Neuron (University of Yale) to determine if activity of this channel is likely to account for changes in AP frequency.

We investigated the effects of hypotonic challenge (280mOsm) on AP frequency within the PVN; AP frequency decreased significantly from 1.0 ± 0.1Hz to 0.5 ± 0.1Hz (n=7; $p<0.01$). The role of TRPV4 was investigated using the agonist 4-α phorbol 12,13-didecanoate (4α-PDD). Application of 1μM 4α-PDD decreased AP frequency to 0.8 ± 0.5Hz (n=6; $p<0.05$), suggesting the presence of TRPV4 channels in neurons within the PVN.

Further investigation was carried out using the TRPV4 specific antagonist RN1734 (5μM). Slices were subjected to hypotonic challenge to ascertain if the patched cell responded and the slice was then treated with RN1734 to inhibit this response. AP frequency decreased during hypotonic challenge to 0.28 ± 0.16Hz and restored to 0.71 ± 0.17Hz upon treatment with RN1734 with no significant difference between AP frequency before hypotonic challenge and with treatment of RN1734 (n=3; $p<0.05$). These results suggest TRPV4 within the neurons of the PVN is involved in volume sensing.